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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/052,547	01/23/2002	Arthur L. Castle	GLC0002-US	1223

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JOHN S. PRATT, ESQ
KILPATRICK STOCKTON, LLP
1100 PEACHTREE STREET
SUITE 2800
ATLANTA, GA 30309

EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/052,547	CASTLE ET AL.	
	Examiner	Art Unit	
	John S. Brusca	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15 and 23-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *2-15 and 23-29* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *2-15 and 25-29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 November 2002 and 23 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/10/02, 3/17/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1 and the carbon tetrachloride species of agene in the election filed 01 December 2003is acknowledged. The traversal is on the ground(s) that the species of creating gene expression profiles is incorrect since the indicated species are related to different steps of the method, rather than being mutually exclusive embodiments. This is found to be persuasive because the amendment filed 01 December 2003 clarifies that contrast analysis, cluster analysis, and principal component analysis, partial least squares analysis, and factor analysis are at least partially drawn to different steps. Upon further consideration the requirement for species election of methods of creating gene expression profiles is withdrawn. In addition, upon further consideration the requirement of election of species of agent is also withdrawn and both acetaminophen and carbon tetrachloride agents will be examined.

The requirement for election between Groups 1 and 2 is still deemed proper and is therefore made FINAL.

The applicants have chosen to cancel claims 16-22 drawn to Group 2 in the amendment filed 01 December 2003.

Claim Objections

2. Claim 25 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The claim depends from cancelled claim 1. For the purpose of examination claim 25 will be considered to depend from claim 2.

3. Claims 26-29 are objected to because of the following informalities: Line 12 of claim 26 is incomplete. Appropriate correction is required. For the purpose of examination line 12 of claim 26 will not be considered.

4. Claims 2-10 and 26-29 are objected to because of the following informalities: The claims are drawn to a method of assessing toxicology of a compound, however toxicology is a branch of science rather than a property of a compound. Appropriate correction is required.

5. Claims 11-15 are objected to because of the following informalities: Claim 11, line 4 recites "a first gene expression levels" and should be amended to be grammatically correct. Claim 11 line 7 recites "second gene expression levels" and should be amended to be grammatically correct. Claim 11 line 6 recites "a second tissue sample" without antecedent basis for a first tissue sample. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 2-10 and 26-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of

experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must practice a method of assessing toxicity of a compound comprising exposing polynucleotides to the compound. Regarding claim 6 one would further have to assess gene response of different genes after their responses were averaged. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The specification does not present guidance to expose polynucleotides to a toxic compound or to assess gene responses after averaging their responses.

c) The specification does not present working examples of exposing a polynucleotide to a toxic compound or to assess gene responses after averaging the responses.

d) The nature of the invention, assessing toxicity of a compound, is complex.

e) Cunningham et al. shows a method of assessing toxicity of a compound by treating animals with the compound and subsequently analyzing mRNA from the animal to assess the effect of the compound on gene expression. The prior art does not show assessment of toxicity by directly exposing polynucleotides to compounds and subsequently monitoring gene expression from the polynucleotides as claimed. The prior art does not show assessment of differences between gene responses after averaging the responses.

f) The skill of those in the art of molecular biology and toxicology is high.

g) It is predictable to one of skill in the art of molecular biology that toxic compounds affect living cell systems rather than isolated polynucleotides, and that assessment of toxic effects requires treatment of cultured cells or cells of an organism to subsequently assess modulation of gene expression by the treated cells. It is predictable that there would be no differences to assess in gene responses if the responses were averaged to be identical.

h) The claims are broad in that they read on a method of assessing toxicity of a compound comprising exposing polynucleotides to the compound, and assessing differences in gene responses that are identical.

The skilled practitioner would first turn to the instant specification to practice the full scope of the claimed invention. However, the specification does not provide guidance or working examples of assessing toxicity of a compound by treatment of polynucleotides with the compound. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art doe not provide guidance to assess toxicity of compounds by treatment of isolated polynucleotides or assessing gene response after averaging the responses. Finally said practitioner would turn to trial and error experimentation to practice the claimed invention. Such represents undue experimentation.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 2-11, 13-15, and 23-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 2-11, 13-15, and 23-29 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is a step of assessing toxicity of a compound.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 2-5, 7-9, 11-14, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al.

The claims are drawn to a method of assessing toxicity of a compound comprising determining the effect of the compound on gene expression and comparing the variability of a composite variable to that of a known toxic compound. In some embodiments the number of genes is greater than 10, a variable is time and dose of the compound, contrast analysis, cluster analysis, and principal component analysis is employed, treated liver, kidney, brain, spleen, pancreas, and lung samples are used, the compound is acetaminophen, and factor analysis is used.

Cunningham et al. shows in columns 1-2 a method of comparing the effect of a known toxic compound and a putative toxic compound on gene expression of a treated cell. Microarray polynucleotide hybridization assays are used to assess gene expression. Preferred tissues are listed as liver, kidney, brain, spleen, pancreas, and lung. A preferred toxic compound is acetaminophen. Cunningham et al. shows SEQ ID NOS: 1-61 on column 4 as targets to be assayed for toxic regulation. Cunningham et al. shows clustering of target genes in column 4. As contrast analysis is defined in the specification on page 8 as analysis of genes that are grouped by their response pattern to the toxic compound, Cunningham et al. shows cluster analysis in Tables 1-3 in columns 14-15. Cunningham et al. shows in column 12 that rats were treated for different times with acetaminophen before sacrifice and mRNA isolation. Time variation is a factor analyzed by Cunningham. Cunningham et al. does not show use of principal component analysis or variation of dose.

Hilsenbeck et al. show in the abstract and throughout the use of principal component analysis to determine those genes that varied the most between two experiments. Hilsenbeck et al. treated mice with breast cancer cells, and then treated the mice with tamoxifen. The mice were sacrificed at various times and mRNA was isolated and analyzed by use of a polynucleotide microarray to assess changes in gene expression during the experiment (see pages 453-454). Hilsenbeck et al. used principal component analysis to determine which genes were the most varied when comparing different mRNA sample sets. Hilsenbeck et al. concludes on page 458 that "principal component analysis of log-transformed data provides a practical approach to data reduction, visualization, and identification of "significant" outlier genes."

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. by use of principal component analysis to analyze the gene expression data because Hilsenbeck et al. shows that principal component analysis can be used to analyze gene expression data of toxicity experiments to determine those gene sets that are most varied by the treatment. It would have been further obvious to vary dose as well as time of treatment to further determine which genes are affected by a toxic compound.

15. Claims 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-5, 7-9, 11-14, 24, and 25 above, and further in view of Holden et al.

The claims are drawn to analysis of the effect of carbon tetrachloride on gene expression.

Holden et al. shows treatment of a hepatoma cell line with carbon tetrachloride, followed by isolation of mRNA and polynucleotide microarray analysis of the effect of carbon

tetrachloride on gene expression in the treated cells. Forty genes were found to be affected. Holden et al states that their method will allow for study of mechanisms of carbon tetrachloride toxicity.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Cunningham et al. in view of Hilsenbeck et al. as applied to claims 2-5, 7-9, 11-14, 24, and 25 above by use of carbon tetrachloride as the assayed compound because Holden et al. shows that carbon tetrachloride is a toxic compound that affects gene expression.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is (517) 272-0714. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (517) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.S. Brusca 20 March 2004

John S. Brusca
Primary Examiner
Art Unit 1631

jsb